Informed Consent for Clinical Research

You will be given a signed copy of this consent form to keep

INSTITUTION: **PAREXEL Baltimore CPRU, Harbor Hospital Center**

INTRODUCTION

We invite you to take part in a research study called "A Randomized, Controlled Study to Evaluate the Short Term Exposure to Smoke Constituents of an Electrically Heated Cigarette Smoking System with Menthol in Adult Smokers During Controlled Smoking". Please take your time to make your decision. Discuss it with your family and friends. It is important that you read and understand several general principles that apply to all that take part in our studies:

(a) Taking part in the study is entirely voluntary;

(b) You will not benefit from the use of the Electrically Heated Cigarette Smoking System (EHCSS) used in this research study. Primarily, knowledge may be gained from your participation that will benefit others;

(c) You may withdraw from the study at any time without losing any of the benefits you are otherwise entitled to.

The nature of the study, the benefits, risks, discomforts and other information about the study is discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you. The Principal Investigator (person in charge of this research study) is Dr. Thomas C. Stock. This research is sponsored by Philip Morris USA (the Sponsor) and PAREXEL International is being paid by the Sponsor to conduct this study.

WHY IS THE STUDY BEING DONE?

This research study is being done to evaluate the short-term exposure to the compounds that make up the smoke of the electrically heated cigarettes in adult smokers during confined smoking. This evaluation will be conducted by measuring identified biomarkers of cigarette smoke exposure in blood and urine and from vital sign measurements. A biomarker is a biological substance or biological effect, which can be measured to evaluate a relationship between a foreign substance, such as cigarette smoke and a body process.

You may not participate in this study if any of the following apply to you:

- You are outside the 21 - 65 years age bracket
- You have not been smoking 10 to 30 menthol cigarettes per day for 12 months prior to study initiation.
- You have used any other nicotine-containing product other than manufactured cigarettes (including roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum, etc.) within 4 weeks prior to study initiation

- You have not smoked Marlboro ULTRA LIGHTS Menthol as your exclusive brand for 4 weeks prior to study initiation

- You have a clinically significant history or evidence (findings from physical examination, clinical laboratory tests, pulmonary function tests, ECG, or vital signs) of abnormalities of body systems/body organs/disease that in the opinion of the Investigator would jeopardize your safety or impact the validity of the study results related to any of the following:

  - **Gastrointestinal** – related to the stomach/intestines and conditions such as bleeding ulcers, inflammatory bowel disease, etc.

  - **Renal** – related to the kidneys and conditions such as kidney stones, etc.

  - **Hepatic** – related to the liver and related conditions such as cirrhosis, etc.

  - **Endocrine** – related to gland function such as diabetes, thyroid disorders, etc.

  - **Oncologic** – related to cancers.

  - **Pulmonary** – related to the lungs/breathing and conditions such as chronic obstructive pulmonary disease and tuberculosis, etc.

  - **Cardiovascular** – related to the heart and blood circulation system, including conditions such as heart attack, abnormal ECG, chest pain, and congestive heart failure, etc.

  - **Neurological** – related to the brain and spinal cord, and conditions such as epilepsy, stroke, multiple sclerosis, seizures, etc.

  - **Psychiatric** – related to the brain in terms of behavior/emotions/addictions such as depression, eating disorders, drug abuse, alcohol abuse, etc.

  - **Hematological** – related to the blood and conditions such as anemia, clotting disorders, etc.

  - **Immunological** – related to the immune system and conditions such as auto immune diseases, AIDS, etc.

- You have any history (current or past) of congestive heart failure.

- You have an active fever of greater than 100.2°F at screening or at check-in.

- You have an acute (sudden onset) illness (e.g. upper respiratory infection, viral infection, etc.) requiring treatment within 2 weeks prior to study initiation.

- You have donated blood of one pint or more or received a whole blood or blood product transfusion within 30 days prior to the study.

- You have donated plasma within seven days prior to the study.

- You have diabetes mellitus that cannot be controlled by diet and exercise alone (i.e. requires treatment with prescription anti-diabetic medication or insulin therapy).
- You require treatment with prescription or over-the-counter bronchodilator medications (e.g. inhaled or oral β-agonists).
- You are currently taking an antibiotic for an acute infection.
- You have had an allergic reaction to local anesthetics (Cetacaine, Xylocaine, Novocaine, etc....)
- You have a history of alcohol and/or drug abuse within the 12 months prior to study initiation.
- You have participated in a previous clinical study for an investigational drug, device, or biological product within 30 days prior to the study.
- You have a positive urine screen for alcohol and/or drugs of abuse.
- You or a first-degree relative (parent, sibling, child) are a current or former employee of the tobacco industry.
- You or a first-degree relative are a current employee of PAREXEL International.
- If female, you are pregnant or nursing, or intend to become pregnant from screening through completion of the study.
- You are 20% below or 30% above the ideal weight for height and estimated frame adapted from the 1983 Metropolitan Life Table. The study staff will determine this.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The research study will involve a total of 44 participants and this is the only place where this study is being performed.

WHAT IS INVOLVED IN THE STUDY?

During the research study you will be asked to visit the research unit for an initial Screening visit to determine your eligibility to take part in the study. If you are eligible to take part, you will then be admitted to the research unit and spend a total of 11 consecutive nights on the unit. While you are confined to the unit you will be a member of one of two groups of smokers. Which group you are in is determined at random (like flipping a coin). One group will be allowed to smoke Marlboro ULTRA LIGHTS Menthol cigarettes and the other group will be allowed to smoke the study cigarettes (ACCORD® JLI Menthol) using the special lighter that allows you to get 8 puffs per cigarette.

During the study, you will never be required to smoke by the study staff. In addition, you may choose to quit smoking at any time. **Subjects who elect to quit smoking may do so and will continue in their assigned group and will finish the study according to the group's schedule.**

If you choose to smoke, you may smoke up to your daily allotment of cigarettes evenly throughout the day and a personal smoking schedule will be created based upon your daily cigarette allowance that is consistent with your usual smoking pattern (number of cigarettes you usually smoke per day). During this time of confinement, various tests will be performed; including physical examination, vital signs (blood pressure, heart rate), blood tests and urine tests. These tests will be described in further detail in this document. You will have an approximate total volume of 385ml (slightly more than 1 ½ cups) of blood samples drawn from Screening to the final post-study tests, if you participate in this study.

Visit One – Screening (up to 28 days prior to treatment)

If you decide to take part in the study, you will be asked to sign this consent form. You may withdraw from the study at any time and for any reason if you want to. You do not have to give a reason to withdraw from the study. If you withdraw from the study at any time, the standard of care that you receive from the clinic will not change.

Once you have signed this consent form you will undergo an evaluation to determine whether or not you are eligible to participate in this study. The evaluation will involve, collection of information which will include demographic information (age, sex, race and other information such as weight and height); vital signs (your temperature, your blood pressure and your heart rate and breathing rate); a medical history; a Smoking History questionnaire; a physical examination; and ECG (electrocardiogram) which is a test that measures your heart function by attaching electrodes (small wires with a sticky backing) to your chest. You will also have collection of blood samples for a full blood count (blood test which will determine the number of different blood cells in your blood), chemistry profile (blood test which measures levels of the other routine chemistry of your blood), blood ethanol test (blood test which measures the any amount of alcohol in your blood) and screen tests for Hepatitis B, Hepatitis C and HIV. If you are female, you will have a pregnancy test performed also. A urine sample will be collected for urinalysis (which will determine what your urine contains), and tested for drugs of abuse (alcohol, amphetamines, opiates, cannabinoids and cocaine). You will also undergo pulmonary functioning testing which is a breathing test to measure the functions of your lungs. After this first clinic visit you will be notified as to your qualification status and an appointment will be scheduled for you to return to the unit to be admitted if you qualify for the study. If you are to be admitted into the study you must have no foods or beverages containing alcohol for 48 hrs prior to study initiation. You must also not engage in any strenuous exercise for 48 hrs prior to and during the confinement period of the study. If you are a woman of childbearing potential (i.e., not surgically sterile by hysterectomy or tubal ligation at least 6 months prior to study participation or at least two years postmenopausal) and sexually active, you must agree to utilize one of the following methods of birth control from screening through completion of the study: barrier contraceptives (condom with spermicide, diaphragm with spermicide), hormonal contraceptives (oral, implant, or injection), IUD, or have a partner who has been vasectomized at least 6 months. Females must also accept the risk that pregnancy might result even while using these methods of birth control. You will be allowed to smoke only at designated times and no smoking will be allowed from 11PM to 7AM during the study. All cigarette butts and used ACCORD® JLI Menthol cigarettes will be collected throughout the study, by study staff.

Day -3

On the evening of Day –3 you will arrive at the study unit for admission. When you are admitted you will be required to give any cigarettes you have to the study staff. You will be allowed to

smoke Marlboro ULTRA LIGHTS Menthol upon request to the study staff until 11PM that evening.

Sometime after you are admitted that evening you will be asked to complete a written form asking about any medications you have taken since you were seen at the Screening visit or if you have experienced any new symptoms (feelings) since the Screening visit. You will have a physical examination (including your temperature, blood pressure and heart rate), an ECG and the same collection of blood and urine tests as you did at Screening – a full blood count, chemistry profile, blood ethanol test, urinalysis and urine testing for drugs of abuse and tobacco. Women will also have a pregnancy test performed.

An evening snack will be provided for you and you may drink water as you wish. Caffeinated beverages are allowed with meals and snacks.

Day –2

Prior to 7AM your vital signs will be measured (blood pressure and heart rate). Starting at 7AM you will be allowed to continue to smoke Marlboro ULTRA LIGHTS Menthol and the study staff will monitor the number of cigarettes you smoke throughout the day to determine your daily allotment of cigarettes for the remainder of the study. Again, the study staff will collect all cigarette butts. You will be allowed to smoke a maximum number + 20% of cigarettes that you reported in your smoking history at Screening. The maximum number of cigarettes you will be allotted is 30 per day.

Again, your breakfast, lunch, dinner and snack will be provided for you on the unit.

Day –1

Prior to 7AM your vital signs will be measured (blood pressure and heart rate). These will be measured again around 12 noon and 8PM.

Again, starting at 7AM you will be allowed to smoke Marlboro ULTRA LIGHTS Menthol cigarettes. For Days –1 through Day 8, with your first cigarette of the morning and your first cigarette after lunch, you will use the Clinical Research Support System Micro (CreSSmicro) Portable Measurement machine to gather smoking topography. This measures things such as the number of puffs you take when smoking the cigarette, the volume of air taken in with the puff, the length of time you puff as well as other more specific information about the puff.

Sometime during the day a physician will perform an exam on your throat to assess your larynx (voice box). This will consist of spraying a local anesthetic (numbing medication) into the back of your throat and the physician using a small mirror to visualize your larynx. This will be repeated on Day 8.

You will have blood samples drawn at various time points across the day to measure biomarkers in your blood which will be looked at throughout the study to determine the effect smoking has on these. You will also have your urine collected 24 hrs/day to test for biomarkers in your urine for the same purpose.

During Day –1 you will be randomized to one of the two smoking groups previously described. You will continue to smoke Marlboro ULTRA LIGHTS Menthol cigarettes until 11PM on Day –1.

Again, your breakfast, lunch, dinner and snack will be provided on the unit.

Day 1
Prior to 7AM your vital signs will be measured (blood pressure and heart rate). Starting at 7AM you will begin smoking the cigarette assigned to your study group (Group A – Marlboro ULTRA LIGHT Menthol or Group B - ACCORD® JLI Menthol EHCSS). Smoking opportunities will be provided approximately every 32 minutes from 7AM through 11PM.

As described in Day –1, smoking topography will be performed with your first cigarette of the morning and your first cigarette after lunch.

Again, blood samples for biomarkers will be collected throughout the day at various time points, and your urine will be collected 24 hrs/day to measure the urine biomarkers.

You will be asked to complete 2 questionnaires if you are in Group B, the ACCORD® JLI Menthol EHCSS group: the ACCORD® JLI Menthol Questionnaire and a Product Assessment Questionnaire.

Again, your breakfast, lunch, dinner and snack will be provided on the unit.

Days 2 – 7
Days 2 through 7 will mirror Day 1

Day 8
Day 8 will mirror Day 1 as well, but additionally, end of study procedures will take place. These will include 3 sets of vital signs (approximately 7AM, 12 noon and 8PM); a physical examination (including weight), a larynx examination, an ECG and additional blood and urine tests.

When all of these procedures are completed on the morning of Day 9, you will be discharged from the research unit.

HOW LONG WILL I BE IN THE STUDY?
You will be in the study approximately 5 ½ weeks from the time of your Screening visit until you are discharged from the unit on the morning of Day 9.
You may be taken out of this study for any of the following reasons: the Investigator feels it is in your medical best interest; the study Sponsor or Investigator wants to stop the study for any reason; or if you are not able to follow the rules set up for this study.

You can withdraw at any time without penalty or loss of benefits to which you are entitled. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor or designee and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?
Potential adverse effects to lung function tests include shortness of breath and dizziness.

Since there is always the possibility that some unexpected adverse effect may develop in some persons participating in the procedures in this study, trained medical personnel are available at Baltimore Clinical Pharmacology Research Unit to provide immediate medical attention.

Cigarette smoking during pregnancy is associated with increased risk of spontaneous abortion, low birth weight infants, and perinatal mortality. Therefore, pregnant women cannot participate in this study and women of childbearing potential must avoid becoming pregnant during the study. Nicotine passes freely into breast milk and a nursing child may receive nicotine from a smoking mother's milk with the possibility of causing harmful side effects to the child. Therefore, women who are nursing cannot participate in this study.

It is possible that checks done during the study may reveal a medical condition that you are currently not aware of (e.g., high blood pressure). If this occurs, your doctor will talk to you about the results and ensure that you are treated properly.

If you have private medical insurance, you should check that your level of coverage would not be affected by taking part in this study.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

You will receive no direct medical benefit from your participation in this study.

WHAT OTHER OPTIONS ARE THERE?

This study is not intended to assess any medical treatment and thus alternative treatment is not appropriate and the only alternative to participating is to not participate. It is up to you to decide whether or not to take part in this study. You do not have to take part if you do not want to and you do not have to give a reason.

WHAT ABOUT CONFIDENTIALITY?

You will be assigned an identification number during your participation in this research study. Information collected during the study will be confidential and retained by PAREXEL and the Sponsor. Your personal information may be disclosed, if required by law. Representatives of the Sponsor, Government Regulatory Agencies such as the Food and Drug Administration of the United States (FDA), as well as the Institutional Review Board (IRB) and/or Ethics Committee may inspect and copy your medical records if you sign this informed consent form to take part in this research study. Records that reveal your identity will be kept confidential by these parties except that, in rare instances, law or judicial process may require revealing your identity to another party. Study information will be collected and may be published, but this will not include your name.

WHAT ARE THE COSTS?

You will not be charged for taking part in this study or for procedures needed because you take part in this study. All study supplies and study procedures are provided to you at no cost.

You or your insurance company will be charged for continuing medical care and/or hospitalization that are not a part of the study.

You will be compensated up to a total of $2000.00 for participating in this study. If you should voluntarily withdraw, or be terminated at the discretion of the Investigator or the Sponsor, you will be compensated for the visits completed at a prorated rate as indicated below.

- You will be compensated $150 for each overnight stay
- $350 Study Completion Bonus

You will receive your entire payment on the day of discharge.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Your participation in this study is entirely voluntary. If you would prefer not to take part you do not have to give a reason. If you do take part, you are free to withdraw from the study at any time without explaining your decision and without any change in the quality or availability of your medical care. Your study doctor may also withdraw you from the study if it is considered to be in your best interest. In addition, the sponsor may end your participation in the study at any time without your consent. You will be told verbally and in writing of any new information or findings that might change your decision to participate in this research study. If new information becomes available, your study doctor or designee will discuss with you whether or not you want to continue in the study. If you decide to continue in the study you will be asked to sign an updated consent form.

If new information becomes available your study doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons for your withdrawal.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the research doctor, Dr. Thomas C. Stock at 1(410) 350-7979 or the clinical research nurse, at 1(410) 350-7979.
For questions about your rights as a research participant, contact the MedStar Research Institute. Direct your questions to:

Dr. Barbara Howard, President, MedStar Research Institute at:

Address:

MedStar Research Institute
Annex #5
108 Irving Street, NW
Washington DC 20010
Telephone: (202) 877-6530
Pager: 1-888-663-6842

SIGNATURES

As a representative of this study, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

_____ _____

Signature of person obtaining the consent Date

I, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and that I will receive a signed copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to participate in this study. I am free to withdraw from the study at any time without need to justify my decision. This withdrawal will not in any way effect my future treatment or medical management. I certify that I am between 21 and 65 years of age. If female, I certify that I am not pregnant and not nursing. I agree to cooperate with Dr. Thomas C. Stock and the research staff and to inform them immediately if I, _____, experience any unexpected or unusual symptoms.

_____

Participant Name (Printed)

_____ _____ _____

Signature of Participant Date Time

_____

Name of Individual Administering Consent (Printed)

_____ _____

Signature of Individual Administering Consent Date

_____

Name of Investigator / Sub-Investigator (if not person obtaining consent) (Printed)

_____ _____

Signature of Investigator / Sub-Investigator (if not person obtaining consent) Date